

Anti-SARS-CoV-2 Antibody Products

Last Updated: February 11, 2021

Summary Recommendations
<ul style="list-style-type: none">• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following products for the treatment of COVID-19:<ul style="list-style-type: none">• COVID-19 convalescent plasma<ul style="list-style-type: none">• The Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the use of convalescent plasma for hospitalized patients with COVID-19 (see Convalescent Plasma for more details).• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins• There are currently insufficient data for the Panel to recommend either for or against the use of the following anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with mild to moderate COVID-19:<ul style="list-style-type: none">• Bamlanivimab• The combination of casirivimab plus imdevimab<ul style="list-style-type: none">• The FDA has issued EUAs for the use of bamlanivimab and the casirivimab plus imdevimab combination for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression (see Anti-SARS-CoV-2 Monoclonal Antibodies for more details).• The FDA also recently issued an EUA for bamlanivimab plus etesevimab for the treatment of certain nonhospitalized patients with mild to moderate COVID-19; the Panel will issue recommendations on the use of this combination shortly.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Convalescent Plasma

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Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.¹

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and nonrandomized studies, observational cohorts, and animal experiments—met the criteria for Emergency Use Authorization (EUA) issuance.^{2,3} Despite meeting the “may be effective” criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of convalescent plasma due to the lack of a randomized, untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population.^{4,5} Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing.

The Panel's assessment of the EAP data is consistent with the FDA statements in the convalescent plasma EUA documents.^{3,6,7}

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Adverse Effects

Before administering convalescent plasma to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank.

The available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for

other indications. These risks include transfusion-transmitted infections (e.g., human immunodeficiency virus [HIV], hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.⁷

Additional risks include a theoretical risk of antibody-dependent enhancement and a theoretical risk of suppressed long-term immunity.

Considerations in Pregnancy

The safety and effectiveness of COVID-19 convalescent plasma during pregnancy have not been evaluated. Several ongoing clinical trials that are evaluating COVID-19 convalescent plasma include pregnant individuals.

Considerations in Children

The safety and effectiveness of COVID-19 convalescent plasma have not been evaluated in pediatric patients. Clinical trials of COVID-19 convalescent plasma in children are ongoing.

Product Availability

On August 23, 2020, the FDA authorized the use of convalescent plasma for the treatment of hospitalized patients with COVID-19.³ Both High Titer (i.e., Ortho VITROS SARS-CoV-2 IgG tested with signal-to-cutoff ratio ≥ 12) and Low Titer COVID-19 Convalescent Plasma are authorized for use.^{6,7} Access to convalescent plasma is no longer available through the Mayo Clinic EAP, which was discontinued on August 28, 2020. Please refer to the [FDA's Recommendations for Investigational COVID-19 Convalescent Plasma website](#) for guidance on the transfusion of investigational convalescent plasma while blood establishments develop the necessary operating procedures to manufacture COVID-19 convalescent plasma in accordance with the Conditions of Authorization set forth in the EUA.

People who have been fully recovered from COVID-19 for ≥ 2 weeks and who are interested in donating plasma can contact their local blood donation or plasma collection center or refer to the FDA's [Donate COVID-19 Plasma](#) website.

Clinical Trials

Randomized clinical trials that are evaluating convalescent plasma for the treatment of COVID-19 are underway; a list is available at [ClinicalTrials.gov](#).

Clinical Data to Date

Open-Label Randomized Clinical Trial of Convalescent Plasma in Hospitalized Patients With Severe or Life-Threatening COVID-19

An open-label randomized clinical trial of convalescent plasma versus standard of care for patients with severe or life-threatening laboratory-confirmed COVID-19 was conducted in Wuhan, China, from February 14 to April 1, 2020. The primary outcome was time to clinical improvement within 28 days. Only plasma units with a SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer of at least 1:640 were transfused. The median time from symptom onset to study randomization was 27 days in the treatment group and 30 days in the control group.⁸

Due to the decreasing incidence of COVID-19 in Wuhan, the trial was terminated early after 103 of the planned 200 patients were enrolled. There was no significant difference between the treatment and control

groups in time to clinical improvement within 28 days (HR 1.40; 95% CI, 0.79–2.49; $P = 0.26$). Among those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference of 23%; OR 1.34; 95% CI, 0.98–1.83; $P = 0.07$). Among those with life-threatening disease, the proportion of patients who showed clinical improvement was similar between the treatment (21%) and control (24%) groups. There was no significant difference in mortality (16% vs. 24% of patients in the treatment and control groups, respectively; $P = 0.30$). At 24 hours, the rates of negative SARS-CoV-2 viral polymerase chain reaction were significantly higher in the convalescent plasma group (45%) than in the control group (15%; $P = 0.003$), and differences persisted at 72 hours.

Limitations

The study was not blinded, and, on average, convalescent plasma was administered approximately 1 month into the disease course. Also, the study was terminated early, and thus lacked sufficient power to detect differences in clinical outcomes between the study groups.

Open-Label Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (ConCOVID Study)

This study has not been peer reviewed.

An open-label randomized clinical trial of convalescent plasma versus standard of care for hospitalized patients with COVID-19 was conducted in 14 hospitals in the Netherlands from April 8 to July 1, 2020. Only plasma confirmed to have anti-SARS-CoV-2 neutralizing antibodies by a SARS-CoV-2 plaque reduction neutralization test (PRNT) and a PRNT50 titer $\geq 1:80$ was transfused. The primary endpoint was in-hospital mortality up to 60 days after admission.

The trial was halted prematurely by the investigators and the study's data safety monitoring board when the baseline SARS-CoV-2 neutralizing antibody titers of participant and convalescent plasma were found to be comparable, challenging the potential benefit of convalescent plasma for the study patient population. Fifty-three of 66 participants had anti-SARS-CoV-2 antibodies at baseline despite being symptomatic for a median time of only 10 days. Among 56 participants whose blood was tested using SARS-CoV-2 plaque reduction neutralization testing, 44 (79%) had neutralizing antibody levels that were comparable to those of 115 donors (median titers of 1:160 vs. 1:160, respectively, $P = 0.40$). When the trial was halted, 86 participants had been enrolled. No differences in mortality ($P = 0.95$), length of hospital stay ($P = 0.68$), or disease severity at Day 15 ($P = 0.58$) were observed between the study arms.⁴

Limitations

The study was terminated early, and thus lacked sufficient power to detect differences in clinical outcomes between the study groups.

Open-Label Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (PLACID Trial)

This study has not been peer reviewed.

An open-label, randomized clinical trial of convalescent plasma versus standard of care for hospitalized patients with COVID-19 was conducted in 39 tertiary care centers in India from April 22 to July 14, 2020. Patients with confirmed COVID-19 and signs of severe disease with hypoxia were eligible if matched donor plasma was available at the time of enrollment. Critically ill patients (those with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [$\text{PaO}_2/\text{FiO}_2$] <200 mmHg or shock) were excluded. The primary outcome was time to disease progression through 28 days (i.e., to $\text{PaO}_2/\text{FiO}_2 <100$ mmHg) or all-cause mortality at 28 days. Participants in the intervention arm received two doses of 200 mL plasma, transfused 24 hours apart. Antibody testing to assess titers of donated plasma

was not available when the trial started.

Four-hundred and sixty-four participants were randomized; 235 were randomized into the convalescent plasma arm and 229 were randomized into the standard of care arm. The arms were well-balanced with regard to age (median of 52 years in both arms) and days from symptom onset to enrollment (median of 8 days in both arms). There was no difference in the primary outcome (time to disease progression and 28-day mortality) across the trial arms. The composite outcome occurred in 44 patients (18.7%) in the convalescent plasma arm and 41 (17.9%) in the control arm. Thirty-four participants (14.5%) in the convalescent plasma arm and 31 patients in the control arm (13.6%) died. In each arm, 17 participants progressed to severe disease (7.2% in the convalescent plasma arm vs. 7.4% in the standard of care arm).⁵

Limitations

SARS-CoV-2 antibody testing was not used to select donated convalescent plasma units; therefore, many participants may have received units with low titers of SARS-CoV-2 neutralizing antibodies. Additionally, the study was not blinded.

Prospective Safety Analyses and Retrospective Exploratory Analyses of Outcomes Among Tens of Thousands of Patients Receiving Open-Label COVID-19 Convalescent Plasma Through the Mayo Clinic Expanded Access Program

The [Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19](#) program was an open-label, nonrandomized EAP that was primarily designed to provide adult patients who have severe or life-threatening (critical) COVID-19 with access to convalescent plasma. Secondary objectives were to obtain data on the safety of the intervention. Exploratory objectives included assessment of 7-day and 28-day mortality. The program was sponsored by the Mayo Clinic and included a diverse range of clinical sites. SARS-CoV-2 antibody testing of plasma donors and assessment of SARS-CoV-2 neutralization potential were not mandated. Patients were transfused with 1 or 2 units (200–500 mL) of convalescent plasma. The main outcomes for the safety analysis were serious adverse events (SAEs), including death; SAEs were reported at 4 hours and at 7 days after transfusion, or as they occurred.^{3,6,9,10}

A peer-reviewed publication described the safety outcomes for the first 20,000 EAP plasma recipients, enrolled between April 3 and June 2, 2020.⁹ One-third of the participants were aged ≥ 70 years, 60% were men, and 71% had severe or life-threatening COVID-19. Twenty percent of the participants were African American, 35% were Hispanic/Latino, and 5% were Asian. Thirteen deaths were assessed as possibly or probably related to the convalescent plasma treatment. The 83 nonfatal SAEs that were assessed as possibly or probably related to the convalescent plasma treatment included 37 TACO events, 20 TRALI events, and 26 severe allergic reactions. The life-threatening events that were reported up to 7 days after transfusion included 87 thrombotic/thromboembolic complications, 406 sustained hypotension events, and 643 cardiac events. The overall mortality rate was 8.6% at 7 days.

Both the FDA and the Mayo Clinic performed retrospective, indirect evaluations of the efficacy of COVID-19 convalescent plasma by using subsets of EAP data, hypothesizing that patients who received plasma units with higher titers of neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower titers of antibodies. This analytic approach was not prespecified in the Mayo Clinic EAP protocol.

The FDA analysis included 4,330 patients, and donor neutralizing antibody titers were measured by the Broad Institute using a pseudovirus assay.⁶ The analysis revealed no difference in 7-day mortality between the patients who received high-titer plasma and those who received low-titer plasma, in the patient population overall, or in the subset of patients who were intubated. However, among nonintubated patients (approximately two-thirds of those analyzed), mortality within 7 days of

transfusion was 11% for those who received high-titer plasma and 14% for those who received low-titer plasma ($P = 0.03$).³ In a post hoc analysis of patients aged <80 years who were not intubated and who were treated within 72 hours of COVID-19 diagnosis, 7-day mortality was lower among the patients who received high-titer plasma than among those who received low-titer plasma (6.3% vs. 11.3%, respectively; $P = 0.0008$).⁶

A similar efficacy analysis by the Mayo Clinic, which has not been peer reviewed, included 3,082 participants who received a single unit of plasma out of the 35,322 participants who had received plasma through the EAP by July 4, 2020. Antibody titers were measured by using the Ortho Clinical Diagnostics COVID-19 IgG assay, and outcomes in patients transfused with low- (lowest 18%), medium-, and high- (highest 17%) titer plasma were compared. After adjusting for baseline characteristics, the 30-day mortality in the low-titer group was 29% and 25% in the high-titer group. This difference did not reach statistical significance. Similar to the FDA analyses, post hoc subgroup analyses suggested a benefit of high-titer plasma in patients aged <80 years who received plasma within 3 days of COVID-19 diagnosis and who were not intubated.¹⁰

Limitations

- The lack of an untreated control arm limits interpretation of the safety and efficacy data. For example, the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded.
- The EAP data may be subject to multiple confounders, including regional differences and temporal trends in the management of COVID-19.
- There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers in convalescent plasma from patients who have recovered from COVID-19 are highly variable.
- The efficacy analyses rely on a subset of EAP patients who only represent a fraction of the patients who received convalescent plasma through the EAP.
- The subgroup that demonstrated the largest estimated effect between high-titer and low-titer convalescent plasma—patients aged <80 years who were not intubated and who were transfused within 3 days of COVID-19 diagnosis—was selected post hoc by combining several subset rules which favored subgroups that showed a trend toward benefit of high-titer plasma. This approach tends to overestimate the treatment effect.
- The FDA analysis relied on 7-day mortality, which may not be clinically meaningful in the context of the prolonged disease course of COVID-19. Because participants in this observational study were not rigorously followed after they were discharged from the hospital, the 30-day mortality estimates are uncertain.

Other Clinical Studies of COVID-19 Convalescent Plasma

The results of retrospective case-controlled studies that evaluated outcomes among COVID-19 convalescent plasma recipients have been published.¹¹ In one such study of patients who were hospitalized between March 24 and April 8, 2020, at Mount Sinai Hospital in New York City, outcomes among 39 consecutive patients who received convalescent plasma with a SARS-CoV-2 anti-spike antibody titer of 1:320 were compared to outcomes among 156 propensity-score-matched controls. As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died ($P = 0.04$, log-rank test), and 72% and 67% of the transfused patients and control patients, respectively, had been discharged from the hospital. Subgroup analyses suggested a benefit of convalescent plasma among patients who were not intubated, had a shorter duration of symptoms, and received therapeutic anticoagulation.

Another study compared convalescent plasma with standard of care in patients with COVID-19 who were hospitalized between March 28 and July 6, 2020, at eight Houston Methodist hospitals. Outcomes for the first 136 convalescent plasma recipients who reached Day 28 post-transfusion were compared with the outcomes for two sets of propensity-score matched controls at 28 days after admission. The analyses suggested a trend towards benefit of convalescent plasma, with larger differences in mortality seen primarily among subgroups of patients who were transfused early (i.e., within 72 hours of admission) with high-titer plasma (i.e., anti-spike protein receptor binding domain titer $\geq 1:1350$).¹²

Other smaller, uncontrolled case series that describe clinical outcomes in patients with COVID-19 have been reported and also suggest that SAEs are uncommon following COVID-19 convalescent plasma treatment.^{1,13-18}

Clinical Data for Other Viral Infections

The use of convalescent plasma has been evaluated for other viral diseases, such as SARS, with some suggestion of potential benefit.¹⁹⁻²¹ The only randomized controlled trial that demonstrated efficacy of convalescent plasma for an infectious disease was conducted more than 40 years ago, for treating Argentine hemorrhagic fever.²² No convalescent plasma products are currently approved by the FDA for the treatment of COVID-19.

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Immunoglobulins: SARS-CoV-2 Specific

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Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins** for the treatment of COVID-19.

Rationale

Currently, there are no clinical data on the use of SARS-CoV-2 immunoglobulins. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants.

Proposed Mechanism of Action and Rationale for Use in Patients with COVID-19

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response. The use of virus-specific immunoglobulins for other viral infections (e.g., cytomegalovirus [CMV] immunoglobulin for the prevention of post-transplant CMV infection and varicella zoster immunoglobulin for postexposure prophylaxis of varicella in individuals at high-risk) has proven to be safe and effective; however, there are currently no clinical data on the use of such products for COVID-19. Potential risks may include transfusion reactions. Theoretical risks may include antibody-dependent enhancement of infection.

Clinical Data

There are no clinical data on the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

Considerations in Pregnancy

Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children

Hyperimmunoglobulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data on their use for other respiratory viruses is limited.

Anti-SARS-CoV-2 Monoclonal Antibodies

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Bamlanivimab and the combination of casirivimab plus imdevimab are anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies available through Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) for the treatment of outpatients with mild to moderate COVID-19 who are high risk for progressing to severe disease and/or hospitalization.

Based on the clinical trial data to date (summarized below), the COVID-19 Treatment Guidelines Panel (the Panel) has determined the following:

- There are currently insufficient data to recommend either for or against the use of bamlanivimab or the casirivimab plus imdevimab combination for the treatment of outpatients with mild to moderate COVID-19. The preliminary data on the use of these agents are from Phase 1 and 2 clinical trials that included relatively few participants and reported only a small number of clinical events related to COVID-19. Final results from large Phase 3 randomized controlled trials will further inform the Panel's recommendations on the use of these monoclonal antibodies.
- Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials, if available, with their patients.
- For high-risk patients who meet EUA criteria for treatment with these monoclonal antibodies, it is appropriate to discuss the potential benefits and risks of the products as part of shared decision making between the patient and the clinician.
- Bamlanivimab and the casirivimab plus imdevimab combination should not be considered standard of care for the treatment of patients with COVID-19.
- There are currently no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab and the casirivimab plus imdevimab combination.
- Patients who are hospitalized because of COVID-19 should not receive bamlanivimab or the casirivimab plus imdevimab combination outside of a clinical trial, although use of the agents can be considered for patients hospitalized for an indication other than COVID-19 who meet EUA use criteria.

Background

The SARS-CoV-2 genome encodes four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) and nonstructural and accessory proteins. The S protein is further divided into two subunits, S1 and S2, that mediate host cell attachment and invasion. Through its receptor-binding domain (RBD), S1 attaches to angiotensin-converting enzyme 2 (ACE2) on the host cell; this initiates a conformational change in S2 resulting in virus-host cell membrane fusion and viral entry.¹

A significant proportion of individuals with COVID-19 produce neutralizing antibodies to SARS-CoV-2 about 10 days after disease onset, with higher antibody levels observed in those with severe disease.² The neutralizing activity of COVID-19 patients' plasma was correlated with the magnitude of antibody responses to SARS-CoV-2 S and N proteins. Monoclonal antibodies targeting the S protein therefore have the potential to prevent SARS-CoV-2 infection and to improve symptomatology and limit progression to severe disease in patients with mild to moderate COVID-19.

Several monoclonal antibodies to SARS-CoV-2 have been developed and characterized.³⁻⁷ Evaluation of their efficacy for the treatment and prevention of COVID-19 is ongoing. In November 2020, the FDA issued two EUAs, one for bamlanivimab and one for the combination of casirivimab plus imdevimab.

The EUAs allow for use of the drugs in nonhospitalized patients (aged ≥ 12 years and weighing ≥ 40 kg) with laboratory confirmed SARS-CoV-2 infection and mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization. Administration of the drugs is recommended as soon as possible after a positive SARS-CoV-2 test result and within 10 days of symptom onset. The issuance of an EUA does not constitute FDA approval.

Bamlanivimab (also known as LY-CoV555 and LY3819253) is a neutralizing monoclonal antibody that targets the RBD of the spike protein of SARS-CoV-2. It is administered intravenously as a one-time dose of bamlanivimab 700 mg.

Casirivimab (previously REGN10933) and imdevimab (previously REGN10987) are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. The combination of these two antibodies blocks the binding of the RBD to the host cell. The monoclonal antibodies are administered intravenously together as a combined one-time dose of casirivimab 1,200 mg and imdevimab 1,200 mg.

Clinical Trial Data to Date

Bamlanivimab

The Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) study is a randomized controlled Phase 2 trial comparing three doses of bamlanivimab to placebo.⁸ An interim analysis of this study suggested a potential clinical benefit of bamlanivimab for outpatients with mild to moderate COVID-19 who received the antibody infusion a median of 4 days after symptom onset. In the pooled bamlanivimab arms, five of 309 participants (1.6%) were hospitalized or had emergency department visits versus nine of 143 participants (6.3%) in the placebo arm. In a subset analysis of patients at high risk for hospitalization (using an expanded definition that approximates the bamlanivimab EUA criteria for treatment), four of 136 participants (2.9%) in the pooled bamlanivimab arms versus seven of 69 participants (10.1%) in the placebo arm were hospitalized or had emergency department visits.⁹

Casirivimab Plus Imdevimab

The [R10933-10987-COV-2067](#) study is a randomized controlled Phase 1 and 2 trial comparing two doses of casirivimab plus imdevimab to placebo. An interim analysis of this study suggested a potential clinical benefit of casirivimab plus imdevimab for outpatients with mild to moderate COVID-19 who received an infusion of the drug combination a median of 3 days after symptom onset.¹⁰ In a post hoc analysis submitted to the FDA for the EUA application, eight of 434 participants (2%) in the pooled casirivimab plus imdevimab arms versus 10 of 231 participants (4%) in the placebo arm were hospitalized or had emergency department visits within 28 days of treatment. Among the participants at higher risk for hospitalization (using the EUA definition of high risk and thus approximating the population that would be recommended for treatment), four of 151 participants (3%) in the pooled casirivimab plus imdevimab arms versus seven of 78 participants (9%) in the placebo arm were hospitalized or had emergency department visits.

A published interim analysis of a subset of 275 participants from the [R10933-10987-COV-2067](#) trial suggests that casirivimab plus imdevimab may have a greater effect in participants who test negative for SARS-CoV-2 serum antibodies (endogenous antibodies) at baseline. In this analysis, the proportion of participants who had at least one COVID-19-related medical visit (including hospitalization or emergency department, urgent care, or physician office/telemedicine visit) was lower in the casirivimab plus imdevimab group (6 of 182 participants [3%] for the pooled doses) than in the placebo group (6 of 93 participants [6%]). In the subgroup of participants who were serum antibody negative at baseline, the

intergroup difference in patients with medical visits was greater (5 of 80 participants [6%] in the pooled antibody group and 5 of 33 participants [15%] in the placebo group).¹¹

Please see [Table 3a](#) for additional information.

Based on these study results, the FDA issued EUAs for the use of these monoclonal antibodies in nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization.

The FDA EUAs do not authorize the use of these antibodies for patients who are hospitalized for COVID-19, although their use can be considered for patients who are hospitalized for a non-COVID-19 indication and meet EUA criteria for use of the products. A substudy of A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (ACTIV-3) randomized patients hospitalized with COVID-19 to bamlanivimab 7,000 mg or placebo, each in addition to remdesivir. On October 26, 2020, following a prespecified interim futility analysis, enrollment into this study was stopped due to lack of clinical benefit.¹² Among 314 adult hospitalized patients (163 in the bamlanivimab arm and 151 in the placebo arm), pulmonary outcomes were similar at Day 5 (odds ratio of being in a more favorable category in the bamlanivimab arm than in the placebo arm 0.85; 95% CI, 0.56–1.29; $P = 0.45$). The time to hospital discharge was also similar in the two arms (rate ratio 0.97; 95% CI, 0.78–1.20).¹³ Patients who are hospitalized for COVID-19 should not receive bamlanivimab or casirivimab plus imdevimab except in a clinical trial. The FDA EUAs do permit the use of these monoclonal antibodies for patients who are hospitalized for an indication other than COVID-19 provided that they have mild to moderate COVID-19 and are at high risk for progressing to severe disease and/or hospitalization.^{14,15}

Rationale for the Panel's Recommendations

In the studies described above, the number of participants was small, and only a limited number of clinical events (e.g., hospitalizations or emergency department visits) were reported. Given the low number of clinical events, it is difficult to draw definitive conclusions about the efficacy of these anti-SARS-CoV-2 antibodies. In addition, if there is a clinical benefit, there is uncertainty as to which patients are most likely to benefit from these antibodies. Although the published data from the bamlanivimab trial indicate that approximately two-thirds of the patients had a high-risk condition, only 10.7% of those in the antibody arm and 14% of those in the placebo arm were aged ≥ 65 years. In the trial supporting the EUA for casirivimab plus imdevimab (see above), only 34% of the participants were considered high risk. Additional clinical trial data are needed to provide further evidence on the safety and efficacy of these agents and to identify the populations in which the potential benefit will be the greatest.

Please see [Table 3a](#) for additional information.

Monitoring

- Bamlanivimab or casirivimab plus imdevimab should only be administered in health care settings by qualified health care providers who have immediate access to medications to treat severe infusion reactions and to emergency medical services.
- Patients should be monitored during infusion of the agents and then observed for at least 1 hour after the infusion is completed.
- No dosage adjustments are required for body weight, renal impairment, or mild hepatic impairment.

Adverse Effects

- In the BLAZE-1 trial, the most common adverse events of bamlanivimab were nausea, diarrhea, dizziness, headache, pruritis, and vomiting. The safety profile of bamlanivimab at all three doses was reportedly similar to that of the placebo.
- Hypersensitivity, including anaphylaxis and infusion reactions, may occur. According to the EUA for bamlanivimab, among >850 participants in ongoing trials who have received bamlanivimab, one anaphylactic reaction and one serious infusion-related reaction occurred and both required treatment, which in one case included epinephrine.
- According to the EUA fact sheet for casirivimab plus imdevimab, among the 533 participants who received casirivimab plus imdevimab in the R10933-10987-COV-2067 trial, one participant had an anaphylaxis reaction that required treatment with epinephrine, and four participants who received the 8,000 mg dose of the combination (casirivimab 4,000 mg and imdevimab 4,000 mg) had an infusion reaction of grade 2 severity or higher, which, in two cases, resulted in permanent discontinuation of the infusion.

Drug-Drug Interactions

- Drug-drug interactions are unlikely between bamlanivimab or casirivimab plus imdevimab and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors, or inducers.
- Please see [Table 3b](#) for more information.
- For persons who received bamlanivimab or casirivimab plus imdevimab for treatment, vaccination with an mRNA COVID-19 vaccine should be deferred for at least 90 days as a precautionary measure to avoid interference of the antibody treatment with vaccine-induced immune responses.¹⁶

Considerations in Pregnancy

- As immunoglobulin (Ig) G monoclonal antibodies, bamlanivimab and casirivimab plus imdevimab would be expected to cross the placenta. There are no available data on the use of bamlanivimab or casirivimab plus imdevimab during pregnancy; however, IgG products are generally not withheld because of pregnancy when their use is indicated.
- Bamlanivimab and casirivimab plus imdevimab should not be withheld from a pregnant individual with COVID-19 who has a condition that poses a high risk of progression to severe COVID-19, and the patient and provider determine that the potential benefit of the drug outweighs potential risk (see the EUA criteria for the use of bamlanivimab and casirivimab plus imdevimab below).
- Inclusion of pregnant people in clinical trials should be encouraged to inform decisions regarding administration of anti-SARS-CoV-2 antibodies to individuals in this population.

Considerations in Children

- Most children with mild or moderate COVID-19, even those with risk factors specified in the EUAs for bamlanivimab or casirivimab plus imdevimab, will not progress to more severe illness and will recover without specific therapy.
- Risk factors for hospitalization in children with COVID-19 have not been clearly defined to the same extent as in adults, making it difficult to identify those at the highest risk of hospitalization and those who would be likely to benefit from use of bamlanivimab or casirivimab plus imdevimab.
- The use of bamlanivimab or casirivimab plus imdevimab for children who meet the EUA criteria

can be considered on a case-by-case basis in consultation with a pediatric infectious disease specialist. Additional guidance is provided in a recent publication endorsed by the Pediatric Infectious Diseases Society.¹⁷

- Additional data on clinical outcomes in children who receive bamlanivimab or casirivimab plus imdevimab for the treatment of COVID-19, including in those with specific risk factors, are needed.

Clinical Trials

- Several clinical trials that are evaluating bamlanivimab, casirivimab plus imdevimab, and other monoclonal antibodies, alone or in combination, for the treatment of COVID-19 are underway or in development. Please see *ClinicalTrials.gov* for the latest information on [bamlanivimab clinical trials](#) and [casirivimab plus imdevimab clinical trials](#).
- Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials with patients who have mild to moderate COVID-19.

Drug Availability

- Bamlanivimab and casirivimab plus imdevimab are available through FDA EUAs for outpatients with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization.
- Given the possibility of a limited supply of bamlanivimab and casirivimab plus imdevimab, as well as challenges of distributing and administering the drug, patients at highest risk for COVID-19 progression should be prioritized for use through the EUA. In addition, efforts should be made to ensure that communities most affected by COVID-19 have equitable access to bamlanivimab and casirivimab plus imdevimab.

High-Risk Criteria for Emergency Use Authorization of Bamlanivimab or Casirivimab Plus Imdevimab

The FDA EUAs allow for the use of bamlanivimab or casirivimab plus imdevimab for the treatment of mild to moderate COVID-19 in nonhospitalized adults and children aged ≥ 12 years and weighing ≥ 40 kg and who are at high risk for progressing to severe COVID-19 and/or hospitalization. High-risk criteria specified in the EUA are:

- Body mass index (BMI) ≥ 35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition
- Currently receiving immunosuppressive treatment
- Aged ≥ 65 years
- Aged ≥ 55 years, *and*
 - Cardiovascular disease, *or*
 - Hypertension, *or*
 - Chronic obstructive pulmonary disease or another chronic respiratory disease.
- Aged 12 to 17 years, *and*

- BMI \geq 85th percentile for their age and gender based on [Centers for Disease Control and Prevention growth charts](#), or
- Sickle cell disease, or
- Congenital or acquired heart disease, or
- Neurodevelopmental disorders, for example, cerebral palsy, or
- A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), or
- Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control.

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Table 3a. Anti-SARS-CoV-2 Monoclonal Antibodies: Selected Clinical Data

Last Updated: February 11, 2021

Study Design	Methods	Results	Limitations and Interpretation
LY-CoV555 (Bamlanivimab) in Outpatients with COVID-19 (BLAZE-1 Interim Analysis)¹			
Double-blind, placebo-controlled, Phase 2 randomized trial in outpatients with mild to moderate COVID-19 (n = 452)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 18 years • Not currently hospitalized • ≥ 1 mild or moderate COVID-19 symptom <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • SpO₂ $\leq 93\%$ on room air, <i>or</i> • Respiratory rate ≥ 30 breaths/min, <i>or</i> • Heart rate ≥ 125 bpm <p>Interventions:</p> <ul style="list-style-type: none"> • Single IV infusion of: <ul style="list-style-type: none"> • BAM 700 mg, <i>or</i> • BAM 2,800 mg, <i>or</i> • BAM 7,000 mg • Placebo • Administered within 3 days after a positive SARS-CoV-2 virologic test result <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mean decrease in NP SARS-CoV-2 VL from baseline to Day 11 (plus or minus 4 days) <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • COVID-19-related hospitalization, ED visit, or death within 28 days of treatment • Safety • Symptom burden 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • BAM (n = 309): <ul style="list-style-type: none"> • BAM 700 mg (n = 101) • BAM 2,800 mg (n = 107) • BAM 7,000 mg (n = 101) • Placebo (n = 143) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age: 45 years in combined BAM arms (range: 18–86 years) vs. 46 years in placebo arm (range: 18–77 years) • Percentage of participants with risk factors for severe COVID-19: 69.6% in combined BAM arms vs. 66.4% in placebo arm • Percentage of participants aged ≥ 65 years: 10.7% in combined BAM arms vs. 14.0% in placebo arm • Median time from symptom onset to infusion of BAM or placebo: 4 days <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • The mean log change in NP SARS-CoV-2 VL from baseline to Day 11 was significantly greater among participants in the BAM 2,800 mg arm than among those in the placebo arm: -0.53 (95% CI, -0.98 to -0.08; $P = 0.02$) • The decline in VL was not significantly different between the BAM 700 mg and BAM 7,000 mg arms and the placebo arm. <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • The number and percentage of participants with COVID-19-related hospitalizations or ED visits within 28 days of treatment was lower among the 	<p>Limitations:</p> <ul style="list-style-type: none"> • Relatively small number of participants in each arm • Low number of hospitalizations or ED visits • NP RT-PCR not a validated surrogate marker of disease progression or recovery • Interim analysis <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to placebo, a single infusion of BAM 2,800 mg hastened decline of VL at Day 11 among outpatients with mild or moderate COVID-19. This treatment effect was not statistically significant for the other BAM doses. • The clinical meaningfulness of this reduction in VL is unclear. • The combined hospitalization or emergency visit rate was lower in the BAM arms than in the placebo arm, but the number of events in each arm was small. Similar rates were seen for all 3 BAM doses. • Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of BAM; data from larger clinical trials are needed.

Study Design	Methods	Results	Limitations and Interpretation
LY-CoV555 (Bamlanivimab) in Outpatients with COVID-19 (BLAZE-1 Interim Analysis)¹, continued			
		<p>BAM recipients than the placebo recipients:</p> <ul style="list-style-type: none"> • All BAM doses: 5 of 309 (1.6%) • BAM 700 mg: 1 of 101 (1.0%) • BAM 2,800 mg: 2 of 107 (1.9%) • BAM 7,000 mg: 2 of 101 (2.0%) • Placebo: 9 of 143 (6.3%) • No deaths reported. • In post hoc analysis of high-risk participants (defined as aged ≥ 65 years or BMI ≥ 35), number and percentage of participants who required hospitalization or ED visit: <ul style="list-style-type: none"> • 4 of 95 (4.2%) in combined BAM arms • 7 of 48 (14.6%) in placebo arm • The change in symptom scores (i.e., improvement from baseline) was slightly better among the BAM recipients than among the placebo recipients. • In the BAM arms, there were no SAEs, and the safety profile of BAM was similar to that of the placebo. 	
LY-CoV555 (Bamlanivimab) in Hospitalized Patients with COVID-19 (ACTIV-3/TICO Preliminary Report)²			
Double-blind, placebo-controlled, randomized trial; a substudy of ACTIV-3/TICO in hospitalized patients with COVID-19 (n = 326)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Adult hospitalized patients • Documented SARS-CoV-2 infection • Duration of COVID-19 symptoms ≤ 12 days <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • End-organ failure <p>Interventions:</p> <ul style="list-style-type: none"> • Single infusion of BAM 7,000 mg • Placebo 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • mITT analysis (n = 314): BAM 7,000 mg (n = 163) and placebo (n = 151) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age: 63 years (range: 50–72 years) in BAM arm vs. 59 years (range: 48–71 years) in placebo arm • Percentage of participants with coexisting illness: 72% in BAM arm vs. 68% in placebo arm • Median days since symptom onset: 7 days (range: 5–9 days) in BAM arm vs. 8 days (range: 5–9 days) in placebo arm 	<p>Limitations:</p> <ul style="list-style-type: none"> • Enrollment was stopped after futility criteria were met, resulting in smaller sample size and limited follow-up period. • Preliminary report <p>Interpretation:</p> <ul style="list-style-type: none"> • No clinical benefit of BAM in hospitalized patients with COVID-19

Study Design	Methods	Results	Limitations and Interpretation
LY-CoV555 (Bamlanivimab) in Hospitalized Patients with COVID-19 (ACTIV-3/TICO Preliminary Report)², continued			
	<ul style="list-style-type: none"> • Participants in both arms received RDV. • All participants received supportive care, which could include supplemental oxygen, and/or glucocorticoids when indicated. <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Early futility assessments: 2 ordinal outcomes at Day 5 (pulmonary and pulmonary-plus) • Efficacy: Time to a sustained recovery defined as hospital discharge to home and remaining at home for ≥ 14 days • Safety: Composite of death, SAE, or incident grade 3 or 4 AE) <p>Secondary Endpoint:</p> <ul style="list-style-type: none"> • Time to hospital discharge 	<ul style="list-style-type: none"> • Percentage of participants receiving RDV: 37% in BAM arm vs. 44% in placebo arm. • 95% of participants began RDV before or on the day of randomization. • Percentage of participants receiving glucocorticoids: 49% in BAM and placebo arms • Percentage of participants requiring supplemental oxygen: <ul style="list-style-type: none"> • None: 27% in BAM arm vs. 28% in placebo arm • <4 L/min: 37% in BAM arm vs. 38% in placebo arm • ≥ 4 L/min: 18% in BAM arm vs. 23% in placebo arm • Noninvasive ventilation or high-flow device: 18% in BAM arm vs. 12% in placebo arm • Median duration of follow-up: 31 days <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • The OR of being in a more favorable pulmonary category in the BAM arm than in the placebo arm was 0.85 (95% CI, 0.56–1.29; $P = 0.45$). • The time to sustained recovery was similar between the arms (rate ratio 1.06; 95% CI, 0.77–1.47). • The percentage of participants with composite safety outcome of death, SAE, or incident grade 3 or 4 AE was 19% in the BAM arm vs. 14% in the placebo arm (OR 1.56; 95% CI, 0.78–3.10). <p>Secondary Outcome:</p> <ul style="list-style-type: none"> • The occurrence of hospital discharge was similar between the 2 arms (rate ratio 0.97; 95% CI, 0.78–1.20). 	<p>Note: The EUA for BAM or CAS plus IMD does not include use in patients hospitalized due to COVID-19.</p>

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067)³			
<p>Double-blind, placebo-controlled, Phase 1 and 2 randomized trial in outpatients with mild to moderate COVID-19 (n = 799)</p> <p>Note: These data are from the FDA EUA for CAS plus IMD.</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Onset of COVID-19 symptoms ≤ 7 days before randomization SpO₂ $\geq 93\%$ on room air <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Hospitalization before or at randomization due to COVID-19 Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 convalescent plasma, IVIG for any indication) <p>Interventions:</p> <ul style="list-style-type: none"> Single IV infusion of CAS plus IMD combination: <ul style="list-style-type: none"> CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg), <i>or</i> CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg) Placebo Administered ≤ 3 days after a positive SARS-CoV-2 virologic test result <p>Primary Endpoint:</p> <ul style="list-style-type: none"> TWA change in NP VL from baseline to Day 7 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> COVID-19-related medical visits including hospitalization or ED, urgent care, or physician office/telemedicine visits within 28 days of treatment Safety Symptom improvement 	<p>Number of Participants:</p> <ul style="list-style-type: none"> CAS plus IMD (n = 533): <ul style="list-style-type: none"> CAS plus IMD 2,400 mg (n = 266) CAS plus IMD 8,000 mg (n = 267) Placebo (n = 266) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age: 42 years (7% aged ≥ 65 years) Percentage of participants with risk factors for severe COVID-19: 34% Median duration of symptoms: 3 days <p>Primary Outcomes:</p> <ul style="list-style-type: none"> Evaluated in the modified full analysis set of participants with detectable virus at baseline (n = 665) TWA change in NP VL at Day 7 was greater among the CAS plus IMD-treated participants overall than among the placebo-treated participants ($-0.36 \log_{10}$ copies/mL; $P < 0.0001$). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> The proportion of participants who had COVID-19-related medical visits within 28 days of treatment was lower in the combined CAS plus IMD arms than in the placebo arm: <ul style="list-style-type: none"> Combined CAS plus IMD arms: 2.8% of patients Placebo arm: 6.5% of patients In a post hoc analysis, the number and percentage of participants who were hospitalized or had a medical visit within 28 days of treatment: <ul style="list-style-type: none"> All CAS plus IMD doses: 8 of 434 (2%) CAS plus IMD 2,400 mg: 4 of 215 (2%) CAS plus IMD 8,000 mg: 4 of 219 (2%) Placebo: 10 of 231 (4%) 	<p>Limitations:</p> <ul style="list-style-type: none"> Relatively small number of participants in each arm Low number of hospitalizations or ED visits NP RT-PCR is not a validated surrogate marker of disease progression or recovery. <p>Interpretation:</p> <ul style="list-style-type: none"> Compared to placebo, a single infusion of CAS plus IMD showed a reduction in VL at Day 7 among outpatients with mild or moderate COVID-19. The clinical meaningfulness of this reduction in VL is unclear. Combined hospitalization or ED visit rate was lower in CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small. Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD; more information is needed.

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067)³, continued			
		<ul style="list-style-type: none"> In a post hoc analysis, the number and percentage of participants at high-risk for progression to severe COVID-19 and/or hospitalization who required hospitalization or ED visit: <ul style="list-style-type: none"> All CAS plus IMD doses: 4 of 151 (3%) Placebo: 7 of 78 (9%) Median time to symptom improvement: <ul style="list-style-type: none"> Combined CAS plus IMD arms: 5 days Placebo arm: 6 days The safety profile of CAS plus IMD was similar to that of placebo. 4 infusion related reactions of grade 2 severity or higher were reported in the CAS plus IMD 8,000 mg arm resulting in permanent discontinuation of the infusion in 2 participants; 1 participant had an anaphylactic reaction that resolved with treatment. 	
Published Preliminary Subset Analysis of REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067 Interim Analysis)⁴ Note: The data presented in this interim analysis represent a subset of participants described in the EUA above.			
Double-blind, placebo-controlled, Phase 1 and 2 randomized trial in outpatients with mild to moderate COVID-19 (n = 275)	Key Inclusion Criteria: <ul style="list-style-type: none"> Onset of COVID-19 symptoms <7 days SpO₂ ≥93% on room air Key Exclusion Criteria: <ul style="list-style-type: none"> Hospitalization before or at randomization due to COVID-19 Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 convalescent plasma, IVIG for any indication) 	Number of Participants: <ul style="list-style-type: none"> All CAS plus IMD doses (n = 182): <ul style="list-style-type: none"> CAS plus IMD 2,400 mg (n = 92) CAS plus IMD 8,000 mg (n = 90) Placebo (n = 93) Participant Characteristics: <ul style="list-style-type: none"> Median age: 44 years (range: 35–52 years) Median time from symptom onset to randomization: 3 days Baseline serum antibody status: <ul style="list-style-type: none"> Positive: 45% of participants Negative: 41% of participants 	Limitations: <ul style="list-style-type: none"> No formal hypothesis testing Interim analysis Relatively small number of participants in each arm These data represent only a subset of participants described in the EUA (above). Low number of medical visits NP RT-PCR is not a validated surrogate marker of disease progression or recovery.

Study Design	Methods	Results	Limitations and Interpretation
Published Preliminary Subset Analysis of REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067 Interim Analysis)⁴, continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • Single IV infusion of CAS plus IMD combination: <ul style="list-style-type: none"> • CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg) or • CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg) • Placebo • Administered ≤3 days after a positive SARS-CoV-2 virologic test result <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • TWA change in NP VL from baseline to Day 7 in participants with negative serum antibody status at baseline <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • COVID-19-related medical visits, including hospitalization or ED, urgent care, or physician office/telemedicine visits within 28 days of treatment • Safety • Symptom improvement 	<ul style="list-style-type: none"> • Unknown: 14% of participants <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Evaluated in modified full analysis set of participants with detectable virus at baseline (n = 221) • TWA change in NP VL at Day 7 was greater among the participants who received CAS plus IMD (-1.74 ± 0.11 log₁₀ copies/mL; CI, -1.95 to -1.53) than among those who received placebo (-1.34 ± 0.13 log₁₀ copies/mL; CI, -1.60 to -1.08). • Among the participants with a negative serum antibody status at baseline, TWA change in VL was greater among those who received CAS plus IMD (-1.94 ± 0.13 log₁₀ copies/mL; CI: -2.20 to -1.67) than among those who received placebo (-1.37 ± 0.20 log₁₀ copies/mL; CI, -1.76 to -0.98). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • Compared to the placebo participants, the CAS plus IMD participants had fewer COVID-19-related medical visits within 28 days of treatment: <ul style="list-style-type: none"> • All CAS plus IMD doses: 6 of 182 (3%) • Placebo: 6 of 93 (6%) • Among participants with negative serum antibody status at baseline, those who received CAS plus IMD had fewer COVID-19-related medical visits within 28 days of treatment: <ul style="list-style-type: none"> • All CAS plus IMD doses: 5 of 80 (6%) • Placebo: 5 of 33 (15%) • The safety profile of CAS plus IMD was similar to that of the placebo; 2 hypersensitivity or infusion related reactions of grade 2 severity or higher were reported in both the CAS plus IMD 8,000 mg arm and the placebo arm. • The mean half-life for both CAS and IMD antibodies ranged from 25–37 days. 	<p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to placebo, a single infusion of CAS plus IMD showed a reduction in VL at Day 7 among outpatients with mild or moderate COVID-19. • The clinical meaningfulness of this reduction in VL is unclear. • The percentage of participants with medical visits was lower in the CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small. • CAS plus IMD may have a greater effect in patients with a negative serum antibody status but further investigation is needed. • Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD; more information is needed.

Key: AE = adverse event; BAM = bamlanivimab; BMI = body mass index; CAS = casirivimab; EUA = Emergency Use Authorization; ED = emergency department; IMD = imdevimab; IV = intravenous; IVIG = intravenous immunoglobulin; mITT = modified intention to treat; NP = nasopharyngeal; RDV = remdesivir; RT-PCR = reverse transcriptase-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO₂ = saturation of oxygen; TWA = time-weighted average; VL = viral load

References

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3. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: <https://www.fda.gov/media/143892/download>. Accessed November 13, 2020.
4. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33332778>.

Table 3b. Characteristics of SARS-CoV-2 Antibody-Based Products Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

- The information in this table is derived from data on the use of these products in investigational trials in patients with COVID-19. The table includes dose recommendations from the FDA EUAs for patients with COVID-19 who meet specified criteria.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the [FDA Medwatch program](#).

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Bamlanivimab (Anti-SARS-CoV-2 Monoclonal Antibody)				
<p>Dose Recommended in an EUA for Nonhospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg) With Mild to Moderate COVID-19 Who are at High Risk for Progressing to Severe COVID-19 and/or Hospitalization:</p> <ul style="list-style-type: none"> • Single dose of BAM 700 mg IV as soon as possible after a positive result on viral test for SARS-CoV-2 and within 10 days of symptom onset (per EUA) 	<ul style="list-style-type: none"> • Nausea • Diarrhea • Dizziness • Headache • Pruritis • Vomiting • Hypersensitivity, including anaphylaxis and infusion reactions • Unexpected SAEs may occur. 	<ul style="list-style-type: none"> • Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. • Monitor patient during the infusion and then observe for ≥1 hour after the infusion is completed. 	<ul style="list-style-type: none"> • Drug-drug interactions are unlikely between BAM and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. 	<ul style="list-style-type: none"> • To date, there are insufficient data for the Panel to recommend either for or against the use of BAM for the treatment of outpatients with mild to moderate COVID-19. • Patients who are hospitalized for COVID-19 should not receive BAM outside of a clinical trial. • A list of clinical trials is available: Bamlanivimab <p>Availability:</p> <ul style="list-style-type: none"> • BAM is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19.¹ See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions.

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)				
<p>Dose Recommended in an EUA For Nonhospitalized Adult and Pediatric Patients (Aged ≥ 12 Years and Weighing ≥ 40 kg) With Mild to Moderate COVID-19 Who are at High Risk for Progressing to Severe COVID-19 and/or Hospitalization:</p> <ul style="list-style-type: none"> CAS 1,200 mg and IMD 1,200 mg IV administered together once in a single dose as soon as possible after positive result on viral test for SARS-CoV-2 and within 10 days of symptom onset (per EUA) 	<ul style="list-style-type: none"> Hypersensitivity, including anaphylaxis and infusion reactions Unexpected SAEs may occur. 	<ul style="list-style-type: none"> Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. Monitor patient during the infusion and then observe for at ≥ 1 hour after the infusion is completed. 	<ul style="list-style-type: none"> Drug-drug interactions are unlikely between CAS plus IMD and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. 	<ul style="list-style-type: none"> To date, there are insufficient data for the Panel to recommend either for or against the use of CAS plus IMD for the treatment of outpatients with mild to moderate COVID-19. Patients who are hospitalized for COVID-19 should not receive CAS plus IMD outside of a clinical trial. A list of clinical trials is available: Casirivimab plus Imdevimab <p>Availability:</p> <ul style="list-style-type: none"> CAS plus IMD is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19.² See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions.
COVID-19 Convalescent Plasma				
1 or more transfusions based on patient response	<ul style="list-style-type: none"> TRALI TACO Allergic reactions Anaphylactic reactions Febrile nonhemolytic reactions Hemolytic reactions Hypothermia Metabolic complications Transmission of infectious pathogens³ Thrombotic events 	<ul style="list-style-type: none"> Before administering convalescent plasma to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank. Monitor for transfusion-related reactions. 	<ul style="list-style-type: none"> Drug products should not be added to the IV infusion line for the blood product. 	<ul style="list-style-type: none"> There are insufficient data for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19. A list of clinical trials is available: COVID-19 Convalescent Plasma

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
COVID-19 Convalescent Plasma , continued				
	<ul style="list-style-type: none"> Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity 	<ul style="list-style-type: none"> Monitor patient's vital signs at baseline and during and after transfusion. 		
SARS-CoV-2 Specific Immunoglobulin				
Dose varies by clinical trial	<ul style="list-style-type: none"> TRALI TACO Allergic reactions Antibody-mediated enhancement of infection Red blood cell alloimmunization Transmission of infectious pathogens 	<ul style="list-style-type: none"> Monitor for transfusion-related reactions. Monitor patient's vital signs at baseline and during and after transfusion. 	<ul style="list-style-type: none"> Drug products should not be added to the IV infusion line for the blood product. 	<ul style="list-style-type: none"> To date, there are insufficient data for the Panel to recommend either for or against the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. A list of clinical trials is available: SARS-CoV-2 Immunoglobulin

Key: AE = adverse event; BAM = bamlanivimab; CAS = casirivimab; CYP = cytochrome P450; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab. 2020. Available at: <https://www.fda.gov/media/143603/download>. Accessed November 13, 2020.
2. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: <https://www.fda.gov/media/143892/download>. Accessed November 13, 2020.
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